

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION See paragraph 2 below

International application No.
PCT/EP2004/008061

International filing date (day/month/year)
16.07.2004

Priority date (day/month/year)
18.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D401/04, C07D295/14, C07D413/10, C07D413/14, C07D403/02, A61K31/4545, A61P25/00

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. The following document has not been furnished:

- copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
- translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
 claims Nos. 16 (industrial applicability)

because:

- the said international application, or the said claims Nos. 16 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos.
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- has not been furnished
 does not comply with the standard

the computer readable form

- has not been furnished
 does not comply with the standard

- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- See separate sheet for further details

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**Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, Inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,17,18
	No:	Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

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Re Item III

Non-establishment of opinion

Claim 16 relates to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of this claim, cf. Article 34(4)(a)(i) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents cited in the search report:

- d1: WO 03/031432 A (BOEHRINGER INGELHEIM INT ; NOVO NORDISK AS (DK)) 17 April 2003 (2003-04-17)
- d2: WO 02/072093 A (SCHERING CORP) 19 September 2002 (2002-09-19)
- d3: WO 02/32893 A (SCHERING CORP) 25 April 2002 (2002-04-25)

2- Novelty

None of the cited documents disclose compounds containing a piperidine substituted in position 4 by a 4-piperidinyloxy moiety. Present compounds of formula (I) are therefore novel at least on account of this structural feature.

Since all the claims relate to the compounds of formula (I), the requirements of Art. 33.2 PCT are met.

3- Inventive step

3.1- The applicant has set himself the task of providing compounds having affinity for the H3 histamine receptor, which are of potential use in the treatment of neurological conditions. D1 and d3 relate to compounds which are H3 receptor ligands.

The compounds of d2 have a dual activity as histamine H3 and m2 muscarinic receptor antagonists.

Taking into account of the activity and of the structures of the compounds disclosed in these documents, it is considered that d1 represents the closest state of the art.

The experimental data disclosed on pages 67 and 68 of the application provide the evidence that present compounds of formula (I) have the claimed activity.

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Accordingly, the objective technical problem can be seen in the provision of further ligands of the histamine H3 receptor.

3.2- Present compounds differ from the compounds of d1 on account of various structural features such as the oxygen binding the piperidine rings, the groups R1 and R2. It appears that even taking into account of the teaching of d2 and d3, the skilled person would not find any hint for preparing the present compounds.

Accordingly the requirements of Art. 33.3 PCT are met.